

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kovesdi et al.

Art Unit: Unassigned

Continuation of U.S. Patent
Application No. 08/258,416

Examiner: Unassigned

Filed: August 21, 2001

For: ADENOVECTOR PHARMACEUTICAL
COMPOSITION

**AMENDMENTS TO SPECIFICATION AND CLAIMS
MADE VIA PRELIMINARY AMENDMENT**

Amendment to Title:

~~COMPLEMENTARY ADENOVIRAL VECTOR SYSTEMS AND CELL LINES~~
ADENOVECTOR PHARMACEUTICAL COMPOSITION

Amendments to specification at page 1, line 1:

This patent application is a continuation of copending U.S. Patent
Application No. 08/258,416, filed June 10, 1994.

Amendments to the claims:

1. — ~~An adenoviral vector that is deficient in two or more adenoviral gene functions.~~

2. — ~~The adenoviral vector of claim 1, wherein at least one of the said two or more gene functions is selected from the group of gene functions comprising the E1, E2, E3 and E4 regions of the adenoviral genome.~~

3. — ~~The adenoviral vector of claim 1, wherein at least one of the said two or more gene functions is selected from the group of gene functions comprising the late regions of the adenoviral genome.~~

4. — The adenoviral vector of claim 2, wherein at least one of the said two or more gene functions is selected from the group of gene functions comprising the late regions of the adenoviral genome.

5. — The adenoviral vector of claim 1, wherein the said two or more adenoviral gene functions is all the adenoviral gene functions.

6. — The adenoviral vector of claim 5, wherein said adenoviral vector comprises adenoviral inverted terminal repeats and one or more adenoviral promoters.

7. — The adenoviral vector of claim 5, wherein said adenoviral vector comprises adenoviral inverted terminal repeats and a packaging signal.

8. — The adenoviral vector of claim 1, wherein said adenoviral vector only functions in a complementing cell line.

9. — The adenoviral vector of claim 8, wherein said adenoviral vector only functions in a complementing cell line as a result of the modification of adenoviral inverted terminal repeats or packaging signal.

10. — A cell line that complements an adenoviral vector of claim 1.

11. — A cell line that complements an adenoviral vector of claim 2.

12. — A cell line that complements an adenoviral vector of claim 3.

13. — A cell line that complements an adenoviral vector of claim 4.

14. — A cell line that complements an adenoviral vector of claim 5.

15. — A cell line that complements an adenoviral vector of claim 6.

16. — A cell line that complements an adenoviral vector of claim 7.

17. — A cell line that complements an adenoviral vector of claim 8.

18. — A cell line that complements an adenoviral vector of claim 9.

19. — A cell line selected from the group consisting of those cell lines designated as 293/E4, 293/ORF-6, and 293/E4/E2A.

20. — A recombinant multiply deficient adenoviral vector of claim 1 comprising a foreign gene.

21. — The recombinant vector of claim 20, wherein said foreign gene is the cystic fibrosis transmembrane regulator gene.

22. — The recombinant vector of claim 20, wherein said recombinant vector is selected from the group consisting of Ad_{GV}-10, Ad_{GV}-11, Ad_{GV}-12, and Ad_{GV}-13.

23. — The recombinant vector of claim 22, wherein said recombinant vector is selected from the group consisting of Ad_{GV}CFTR.10, Ad_{GV}CFTR.11, Ad_{GV}CFTR.12, and Ad_{GV}CFTR.13.

24. — A recombinant multiply deficient adenoviral vector of claim 1 comprising a DNA sequence capable of expressing in a mammal a therapeutic agent.

25. — The recombinant multiply deficient adenoviral vector of claim 24, wherein said therapeutic agent is an antisense molecule selected from the group consisting of mRNA and a synthetic oligonucleotide.

26. — A recombinant multiply deficient adenoviral vector of claim 1 comprising a DNA sequence capable of expressing in a mammal a polypeptide capable of eliciting an immune response to said polypeptide.

27. — A method of gene therapy comprising the administration to a patient in need of gene therapy a therapeutically effective amount of a recombinant multiply deficient adenoviral vector of claim 20.

28. — ~~A method of gene therapy comprising the administration to a patient in need of gene therapy a therapeutically effective amount of a recombinant multiply deficient adenoviral vector of claim 21.~~

29. — ~~A method of gene therapy comprising the administration to a patient in need of gene therapy a therapeutically effective amount of a recombinant multiply deficient adenoviral vector of claim 22.~~

30. — ~~A method of gene therapy comprising the administration to a patient in need of gene therapy a therapeutically effective amount of a recombinant multiply deficient adenoviral vector of claim 23.~~

31. — ~~The method of claim 28, wherein the recombinant multiply deficient adenoviral vector is administered to the lungs of said patient.~~

32. — ~~The method of claim 30, wherein the recombinant multiply deficient adenoviral vector is administered to the lungs of said patient.~~

33. — ~~A method of therapy comprising the administration to a patient in need of therapy a therapeutically effective amount of a recombinant multiply deficient adenoviral vector of claim 1 comprising a DNA sequence capable of expressing a therapeutic agent.~~

34. — ~~The method of claim 33, wherein said therapeutic agent is an antisense molecule selected from the group consisting of mRNA and a synthetic oligonucleotide.~~

35. — ~~A method of vaccination comprising the administration to a patient in need of vaccination an immunity inducing effective amount of a recombinant multiply deficient adenoviral vector of claim 1 comprising a DNA sequence capable of expressing a polypeptide capable of eliciting an immune response to said polypeptide.~~

36. A pharmaceutical composition comprising recombinant adenoviral vectors and a pharmaceutically acceptable carrier, wherein each recombinant adenoviral vector is deficient in one or more essential gene functions of one or more regions of the adenoviral genome selected from the group consisting of the E1, E2A, and E4 regions of the adenoviral genome, and wherein the pharmaceutical composition does not contain replication-competent adenoviruses.

37. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E1.

38. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E2A.

39. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E4.

40. The composition of claim 36, wherein the adenoviral vector is deficient in two or more essential gene functions.

41. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E2A regions of the adenoviral genome.

42. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E4 regions of the adenoviral genome.

43. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E2A and E4 regions of the adenoviral genome.

44. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene function of each of three regions of the adenoviral genome.

45. The composition of claim 44, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1, E2A, and E4 regions of the adenoviral genome.

46. The composition of claim 36, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

47. The composition of claim 37, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

48. The composition of claim 38, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

49. The composition of claim 39, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

50. The composition of claim 40, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

51. The composition of claim 41, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

52. The composition of claim 42, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

53. The composition of claim 43, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

54. The composition of claim 44, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

55. The composition of claim 45, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

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For: ADENOVECTOR PHARMACEUTICAL
COMPOSITION

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to the examination of the above-identified patent application, please enter the following amendments and consider the following remarks.

AMENDMENTS

IN THE TITLE:

Replace the title with:

ADENOVECTOR PHARMACEUTICAL COMPOSITION

IN THE SPECIFICATION:

At page 1, line 1, insert:

This patent application is a continuation of copending U.S. Patent
Application No. 08/258,416, filed June 10, 1994.

IN THE CLAIMS:

Please cancel claims 1-35 and add the following claims:

36. (New) A pharmaceutical composition comprising recombinant adenoviral vectors and a pharmaceutically acceptable carrier, wherein each recombinant adenoviral vector is deficient in one or more essential gene functions of one or more regions of the adenoviral genome selected from the group consisting of the E1, E2A, and E4 regions of the

adenoviral genome, and wherein the pharmaceutical composition does not contain replication-competent adenoviruses.

37. (New) The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E1.

38. (New) The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E2A.

39. (New) The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E4.

40. (New) The composition of claim 36, wherein the adenoviral vector is deficient in two or more essential gene functions.

41. (New) The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E2A regions of the adenoviral genome.

42. (New) The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E4 regions of the adenoviral genome.

43. (New) The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E2A and E4 regions of the adenoviral genome.

44. (New) The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene function of each of three regions of the adenoviral genome.

45. (New) The composition of claim 44, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1, E2A, and E4 regions of the adenoviral genome.

46. (New) The composition of claim 36, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

47. (New) The composition of claim 37, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

48. (New) The composition of claim 38, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

49. (New) The composition of claim 39, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

50. (New) The composition of claim 40, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

51. (New) The composition of claim 41, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

52. (New) The composition of claim 42, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

53. (New) The composition of claim 43, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

54. (New) The composition of claim 44, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

55. (New) The composition of claim 45, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

REMARKS

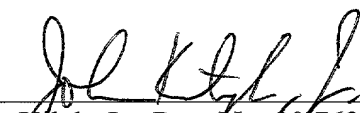
The title has been amended to replace the existing title with a title that is more descriptive of the pending claims. The specification has been amended to indicate that the instant application is a continuation of a U.S. Patent Application No. 08/258,416. Claims 1-35 have been cancelled and claims 36-55 have been added. New claims 36-55 are supported by the claims as originally filed and by the specification in its entirety and, in particular, at page 11, lines 26-31, page 14, lines 8-17, and page 17, lines 6-15.

Please note that the new claims 36-55 are identical to issued claims 1-20 of U.S. Patent No. 5,994,106 (which issued from a continuation of the same parent patent application), except that the new claims are in the form of a "pharmaceutical composition" rather than a "stock." A copy of U.S. Patent No. 5,994,106 is enclosed herewith for the convenience of the Examiner.

In re Appln. of Kovesdi et al
Continuation of U.S. Application No. 08/258,416

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: August 21, 2001

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For: **ADENOVECTOR PHARMACEUTICAL
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PENDING CLAIMS AFTER ENTRY OF PRELIMINARY AMENDMENT

36. A pharmaceutical composition comprising recombinant adenoviral vectors and a pharmaceutically acceptable carrier, wherein each recombinant adenoviral vector is deficient in one or more essential gene functions of one or more regions of the adenoviral genome selected from the group consisting of the E1, E2A, and E4 regions of the adenoviral genome, and wherein the pharmaceutical composition does not contain replication-competent adenoviruses.

37. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E1.

38. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E2A.

39. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene functions of E4.

40. The composition of claim 36, wherein the adenoviral vector is deficient in two or more essential gene functions.

41. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E2A regions of the adenoviral genome.

42. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1 and E4 regions of the adenoviral genome.

43. The composition of claim 40, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E2A and E4 regions of the adenoviral genome.

44. The composition of claim 36, wherein the adenoviral vector is deficient in one or more essential gene function of each of three regions of the adenoviral genome.

45. The composition of claim 44, wherein the adenoviral vector is deficient in one or more essential gene functions of each of the E1, E2A, and E4 regions of the adenoviral genome.

46. The composition of claim 36, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

47. The composition of claim 37, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

48. The composition of claim 38, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

49. The composition of claim 39, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

50. The composition of claim 40, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

51. The composition of claim 41, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

52. The composition of claim 42, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

53. The composition of claim 43, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

54. The composition of claim 44, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.

55. The composition of claim 45, wherein the adenoviral vector is prepared in a cell that complements in *trans* the deficient essential gene functions of the adenoviral vector, wherein the genome of the cell line is free of overlapping sequences with the adenoviral vector that are sufficient to mediate a recombination event resulting in a replication competent adenoviral vector.